REMARKS

The withdrawal of all of the previous grounds of rejection and the indication of allowability of claims 1-5, 7 and 13 is respectfully acknowledged. It is believed in view of the above amendments and following remarks that all current claims should be allowable.

The Amendments

Claims 15 and 16 are amended to address the 35 U.S.C. §112, second paragraph, rejections. Claim 15 is amended to recite the positive step that the active compound is formulated together with at least one pharmaceutically acceptable excipient. Claim 16 is amended to recite this aspect as well, thus, it has an additional limitation relative to claim 1. See, e.g., page 23, line 27, to page 24, line 10, supporting these amendments. The amendments do not narrow the scope of the broadest claims.

Applicants reserve the right to file one or more continuing and/or divisional applications directed to any subject matter disclosed in the application which may have been canceled by any of the above amendments.

The Rejection under 35 U.S.C. §112, first paragraph

The rejection of claim 9 under 35 U.S.C. §112, first paragraph, as lacking adequate enablement is respectfully traversed.

The Office action alleges that the specification is not enabling for using the compounds to treat an impairment of learning and/or memory which is a consequence of Alzheimer's disease. Applicants had limited the claims to treating an impairment of learning and/or memory which is a consequence of Alzheimer's disease in view of the comments in the Office action of March 25, 2010 (bottom of page 3) which appeared to indicate the claims were enabling for this more limited scope. It is noted that claim 9 was indicated as allowable in that Office action. Applicants believe their disclosure together with the evidence showing the knowledge of one of ordinary skill in the art (which must be considered for enablement purposes) established enablement for current claim 9. However, additional evidence in support thereof is provided here.

As previously established, and not disputed, applicants disclosure provides a sufficient showing that a representative sample of the claimed compounds:

- exhibit PDE9A-inhibiting activity (results of the assays at pages 17-19),
- provide for increase in intracellular neuronal cGMP concentration in cell cultures (pages 19-20 of applicants' specification),
- provide for long term potentiation regarded as a cellular correlate of learning and memory processes (pages 20-21 of applicants' specification), and
- lead to advantageous results in the social recognition test (pages 21-22 of applicants' specification).

Further, applicants have provided examples of literature references which show the acceptance in the art that there is a nexus between these properties and use in carrying out the claimed methods, i.e., treating an impairment of learning and/or memory, particularly connected with Alzheimer's disease.

It is alleged in the Office action that applicants' evidence does not support that these aspects were known in the art prior to applicants' US filing, i.e., prior to Aug. 31, 2005. Applicants respectfully disagree. While the Van der Staay reference that was referred to was published after this date, it does review previous developments and the Introduction section of Van der Staay refers to a number of pre-2005 references to support the position applicants have taken regarding the knowledge of one of ordinary skill in the art. See, particularly, the citation of the Gong et al. (2004), Barad et al. (1998) and Zhou et al. (1994) references for the connection of PDE inhibition and Alzheimer's disease treatment. Referring to this previous work, Van der Staay states (page 908): "Over the years, convincing experimental evidence has accumulated supporting the cognition-enhancing properties of several classes of PDE inhibitors." Additionally, most of the other references which applicants cited to support their position are prior to applicants' filing date. See the discussion below.

The evidence of record supports that one of ordinary skill in the art would have a reasonable expectation that compounds having the activity described in the specification and shown in the assays in the specification would be useful in methods for treating an impairment of learning and/or memory which are a consequence of Alzheimer's disease. It was known at the time of the invention that the glutamatergic system in the brain is deeply involved in learning and memory processes in the hippocampus and cortex of rodents, but also of primates and humans. This can be proven by the memory deficits which are induced by systemic administration of NMDA-receptor antagonists (a specific glutamate receptor), such as phencyclidine, MK-801 or ketamine. Compounds which are able to facilitate

glutamatergic neurotransmission can therefore enhance cognitive processes in diseases which have a dysfunction of the glutamatergic system. The learning and/or memory impairments – such as associated with Alzheimer's Disease and the other causes described in the specification – are related to such dysfunctional glutamatergic neurotransmission in the brain; see, e.g., the pre-2005 previously cited articles of Francis et al., *Int. J. Geriatric Psych.*, vol. 18, S15-21 (2003); and Francis et al., *J.Neurochem.*, vol. 60, no. 5, pp. 1589-1604 (1993). The postsynaptic glutamatergic processes are linked to the NO/cGMP/cGK/CREB pathway which is involved in synaptic plasticity and learning and memory processes on a molecular level; see, e.g., Puzzo et al., *J. Neurosci.*, vol. 25(29), pp. 6887-6897 (July 2005) (previously cited, copy provided again). Therefore, compounds enhancing cGMP levels in glutamatergic neurons, such as PDE9-inhibitors, are able to treat impairments of cognitive processes of memory deficits linked to a dysfunctional glutamatergic system, in general. The advantageous activity of the compounds for such use is not dependent on the cause of the impairment due to this general effect. The properties of PDE9-inhibitors for treating learning and/or memory impairments are shown by long-term potentiation experiments in-vitro and efficacy in the social recognition test in-vivo. Test paradigms have been shown to be dependent on functional NO/cGMP/cGK/CREB systems; see, e.g., Puzzo, cited above. Taken together, compounds like PDE9-inhibitors showing efficacy in the mentioned test paradigms (i.e. long-term potentiation and social recognition test) would be reasonably expected to be of therapeutic benefit for treating learning and/or memory impairments linked to a dysfunctional glutamatergic system, as described by the current invention. In summary, the prior art before Aug. 2005 provides a reasonable showing of a nexus between the type of physiological activity shown for the compounds (or readily verifiable by the assays provided in the specification) and the use for treating learning and/or memory impairments, particularly in connection with Alzheimer's disease.

Furthermore, applicants refer to the newly provided Andreeva et al. reference (copy attached, published 2001). This reference further confirms the role of cGMP in memory processes. See, e.g., page 9073, right hand column, last paragraph, stating: "NO and cGMP also appear to act as synaptic signaling agents in the hippocampus and cerebellum. They are involved in longterm depression (LTD) (Hartell, 1996) as well as long-term potentiation (LTP) (Schuman and Madison, 1991; Chetkovich et al., 1993; Selig et al., 1996; Son et al., 1998) and thus may play an important role in the biochemical mechanisms of learning and

memory." See also, page 9074 last paragraph – 9075, stating:

> This may indicate that PDE9A, which is IBMX insensitive but zaprinast-sensitive, may be involved in this synaptic response and that cGMP accumulation is associated with synaptic depression at this synapse. cGMP-regulated processes in the hippocampus play an important role in the early stages of memory consolidation (Bernabeu et al., 1996). Using a passive avoidance task, it was observed that the level of cGMP in the hippocampus increased immediately after training and that administration of an analog of cGMP into the hippocampus immediately after training enhanced memory performance. In addition, infusion of an sGC inhibitor immediately after training caused full elimination of the training effect (Bernabeu et al., 1997). In another study, the effects of 7-nitroindazole, a selective inhibitor of nNOS, and zaprinast were evaluated in an object recognition task in rats based on the differential exploration of new and familiar objects (Prickaerts et al., 1997). 7-Nitroindazole impaired the discrimination between objects, whereas zaprinist facilitated object recognition and restored the recognition deficit caused by 7-nitroindazole. These data suggest that the NO-cGMP signal transduction pathway is involved in memory formation in this task and that PDEs hydrolyzing cGMP, in particular PDE9A, which is expressed in the CA1 pyramidal neurons of the hippocampus, may participate as important determinants of intracellular cGMP concentration. Thus, in the basal forebrain, olfactory bulb, cerebellum, and hippocampus, regions known to be associated with behavioral state regulation, olfaction, motor control, and learning, the NO-cGMP signaling pathway appears to play an important role. In these regions we have found strong expression of PDE9A. We therefore propose that in these regions and in the functions subserved by these regions, PDE9A is important because its high affinity for cGMP makes it a major regulator of intracellular cGMP concentration. Determining the precise cellular localization of PDE9A and the mechanisms underlying the regulation of its expression and activity will be crucial in understanding the exact physiological role of this enzyme."

The document stresses the role of PDE9 in memory processes and points to the role of zaprinast (which interacts with PDE9) in recognition. Thus, further pre-filing support for the nexus between the properties of PDE9 inhibition and increase in intracellular neuronal cGMP concentration in cell cultures exhibited by the compounds and treatment of memory impairment is provided.

The Examiner points out that evidence was provided by the PTO as well and refuted applicants' allegation (from two replies previous) that the PTO provided no evidence. Applicants note that no references were cited in the Office action prior to this statement by

applicants (see Office action of July 29, 2009). However, applicants note that two webpages were cited in support of the PTO position in the previous Office action to that. Thus, applicants retract their statement that no evidence has been provided. Applicants do, however, urge that the burden of proof lies with the PTO to prove enablement (see, e.g., MPEP §2164.04 citing In re Marzocchi et al., 169 USPQ 367 (CCPA 1971)) and that the evidence provided by applicants more strongly supports their position than the evidence provided by the PTO. The PTO evidence on this issue appears to be reference to two websites one of whose content may be of dubious source (wikipedia). Further, the website nature of the material makes the dates of this evidence impossible to verify. That Office action also cites to a statement from U.S. Patent No. 7,067,507 referring to an alleged failure of progress in previous treatment attempts. Applicants urge, however, that this is a non-verified self-serving statement provided in many patent applications. Applicants, to the contrary, have cited to peer-reviewed scientific articles.

It is further alleged in the Office action that "only two kinds of drugs ever emerged" for such treatments. No documentary evidence is provided for this statement or to explain it. If this is meant to state that there are only two approved drugs for marketing for such treatment, applicants urge that this fails to support a lack of enablement. The enablement standard does not require that the compounds be shown to be approved by the FDA to give a reasonable basis for enablement. The PTO has the burden of proof and must establish that – based on the disclosure and what was known to one of ordinary skill in the art at the time of the invention – one of ordinary skill in the art would not have had a reasonable expectation that the compounds would have some activity for treating an impairment of learning and/or memory which is a consequence of Alzheimer's disease. Applicants are not required to support that the compounds would provide a cure or provide a certain high level of activity or provide an activity which would support FDA approval for marketing the drug for such use.

It is further argued in the Office action that there is no good physiological test for Alzheimer's disease, that one must rely on assorted psychological tests to diagnose Alzheimer's disease and that Alzheimer's disease can only be diagnosed post mortem. No evidence is cited to support these allegations. Applicants would submit that, unfortunately, people are diagnosed with Alzheimer's everyday and were prior to 2005. The means of diagnosis are sufficient enough for the medical community and for one of ordinary skill in the art. Further, applicants fail to see how these allegations support a case for non-enablement.

The question is whether the available tests (whether physiological or psychological) provide a tool which is accepted in the art as indicative of improvement of the condition. The pre-filing literature of record (discussed above) makes clear that the known psychological tests, such as the social cognition test, are accepted in the art for assessing impairment of learning and/or memory and, thus, the effectiveness of a treatment thereof. Of course, researchers are always looking for improved tests but that does not mean that the existing tests are not useful for assessing the condition. There is no basis on the record to support the PTO's position that the existing psychological tests, such as the social cognition test, are not effective for assessing impairment of learning and/or memory. To the contrary, the only evidence of record supports that such tests are relied on by those skilled in the art for such assessment. This is of particular relevance in the current context because applicants' describe in the specification that the compounds of their invention show an advantageous effect in an accepted animal model of the social cognition test (i.e., at pages 21-22). The specification here also describes why this test is useful for assessing impairment of learning and/or memory. The showing of the effectiveness of the compounds in an accepted animal model recognized in the art as useful for assessing impairment of learning and/or memory strongly supports enablement of the current claims.

In view of the evidence submitted by applicants, their comments on the Wands factors are re-emphasized below. These factors also support a finding of enablement.

- Amount of Guidance – As pointed out above, applicants' disclosure provides guidance regarding the physiological activity and assays for determining such activity which have a nexus to use in carrying out the claimed methods.
- Unpredictability in the Art – No allegation has been made that the this art area is one that is particularly unpredictable. Further, the standard for enablement is not absolute predictability but only reasonable expectation of success; see In re Wright, 999 F.2d 1557, 27 USPQ2d 1510,1512 (Fed.Cir. 1993).
- Number of Working Examples – The results of the assay at pages 17-19 showing PDE9A-inhibiting effect for the compounds of the invention are working examples. The results of the three following assays at pages 19-22 are also working examples of the physiological effect which has a nexus to use in carrying out the claimed methods.
- Nature of the Invention – The nature of the invention provides no implication of non-enablement.

- State of the Prior Art – The novelty of the invention (as indicated by the otherwise allowability of the claims) does not create any presumption of non-enablement. To the contrary, as pointed out above, the burden lies first with the PTO to provide evidence or objective reasoning substantiating the allegation that the enabling disclosure is not commensurate in scope with the claims; see, e.g., MPEP §2164.04 citing Marzocchi et al., cited above. The evidence of record, considered as a whole, is not believed to refute the inventors' disclosure – and other supporting evidence – that the compounds would be useful in the claimed methods.
- Level of Skill in the Art – Applicants strongly disagree with the previous allegation that the level of skill of one of ordinary skill in this art is low. The level of skill is not an assessment of what has been accomplished in the effort. It is the level of the skill of those in the art working to solve the problem. That, historically, the disease or condition has been difficult to treat is not indicative of a low level of skill. To the contrary, the difficulty of treating the disease or condition – and the high impact of finding a treatment – means that those of very high skill level are working on the solution. Those working to find treatments as stated in the instant claims are Ph.D. level researchers at the highest level.
- Breadth of the Claims – The breadth of the claims is quite focused here. The compounds used for the methods are very well characterized and of a specific scope and the method is for treating conditions associated specifically with Alzheimer's disease. Such specificity in the breadth of claims here supports a finding of enablement.
- Amount of Experimentation – The amount of experimentation required was not addressed in the Office action. However, even if some further experimentation is required, such does not equate to **undue** experimentation or lack of enablement. Where the experimentation required is merely routine experimentation to one of ordinary skill in the art, it is not undue experimentation and does not support a case for lack of enablement. See, e.g., In re Wands, 858 F.2d at 736-37, 8 USPQ2d at 1404, stating: "Enablement is not precluded by the necessity for some experimentation ... . However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation'." See also Ex parte Jackson, 217 USPQ 804 (Bd. Pat. App. 1982), stating: "The

determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art ... The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed."

For all of the above reasons, it is urged that one of ordinary skill in the art is adequately taught by applicants' specification – taken in view of the knowledge of one of ordinary skill in the art – how to carry out the claimed invention. Thus, the claims are enabled and the rejection under 35 U.S.C. §112, first paragraph, should be withdrawn.

The Rejection under 35 U.S.C. §112, second paragraph

The rejection of claim 15 under 35 U.S.C. §112, second paragraph, is believed to be rendered moot by the above amendment. Claim 15 now recites the positive step of formulating the active compound with at least one pharmaceutically acceptable excipient. Thus, it provides a method step and does not merely recite an intended use. Applicants urge that the rejection should be withdrawn.

The Double Patenting Rejection

The rejection of claim 16 for double patenting is believed to be rendered moot by the above amendment. Claim 16 now requires at least one pharmaceutically acceptable excipient in the composition. Thus, it is further limiting of claim 1 and not a duplicate of claim 1. Applicants urge that the rejection should be withdrawn.

It is submitted that the claims are in condition for allowance. However, the Examiner is kindly invited to contact the undersigned to discuss any unresolved matters.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

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